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Dithiophosphorylation of Paracetamol

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Abstract—Paracetamol smoothly reacted with 2,4-diaryl-1,3,2λ^5,4λ^5-dithiadiphosphetane 2,4-disulfides to give *O*-[4-(acetylamino)phenyl] hydrogen arylphosphonodithioates.

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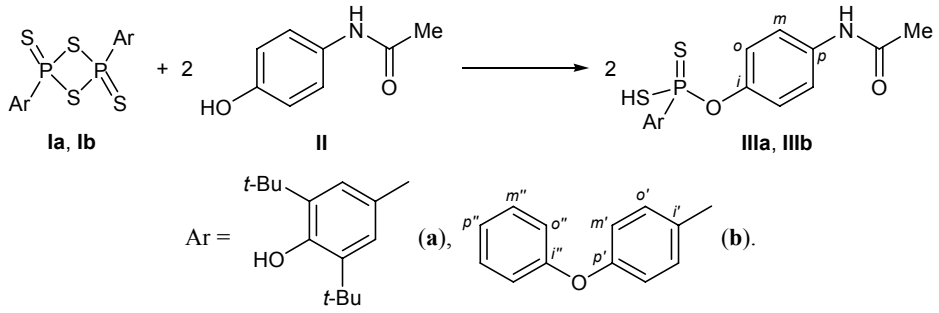
Phenols are widely used in medical practice as antiseptics and are starting compounds for the introduction of pharmacophoric aryl fragments into molecules of potentially biologically active organophosphorus compounds. Reactions of phenols with 1,3,2λ^5,4λ^5-dithiadiphosphetane 2,4-disulfides yield *O*-phenyl hydrogen phosphonodithioates [1, 2]. Nevertheless, dithiophosphorylation of phenols containing pharmacophoric groups has received insufficient attention. With the goal of extending the series of biologically active compounds which could find application as antimicrobial agents, in the present article we describe a new version of synthesis of dithiophosphonic acid derivatives via reactions of 2,4-diaryl-1,3,2λ^5,4λ^5-dithiadiphosphetane 2,4-disulfides with functionally substituted phenols which are already used as active substances in medicines. An example of known pharmacologically active phenols is paracetamol which is used as antipyretic and analgesic. Reactions of paracetamol with phosphorus sulfides have not been reported so far.

We have found that 2,4-diaryl-1,3,2λ^5,4λ^5-dithiadiphosphetane 2,4-disulfides **Ia** and **Ib** smoothly react with paracetamol (**II**) in benzene at 20–45°C (reaction time 1 h) to produce crystalline *O*-[4-(acetylamino)-phenyl] hydrogen arylphosphonodithioates **IIIa** and **IIIb** (Scheme 1). The ^{31}P–{^{1}H} NMR spectra of dithiophosphonates **IIIa** and **IIIb** contained only one signal at δ_P 89.7 or 78.9 ppm, respectively. In the IR spectrum of **IIIa**, the amide carbonyl stretching vibration band (amide I) was observed at 1629 cm^{-1}, and absorption band due to bending vibrations of the N–H bond (amide II) appeared at 1587 cm^{-1}. Compounds **IIIa** and **IIIb** displayed in the ^{1}H NMR spectra singlets at δ 2.21 (**IIIa**, $CDCl_3$) and 2.65 ppm (**IIIb**, acetone-d_6) from the methyl protons in the acetyl group. In the ^{13}C NMR spectrum of **IIIb** recorded from a solution in acetone-d_6 with decoupling from protons, the carbonyl carbon nucleus resonated as a singlet at δ_C 167.4 ppm. The mass spectra of **IIIa** and **IIIb** (electron impact) contained the molecular ion peaks with *m*/*z* 451.26 and 415.91, respectively.

Scheme 1.



Thus, smooth reaction of paracetamol with 2,4-diaryl-1,3,2λ^5,4λ^5-dithiadiphosphetane 2,4-disulfides provides a synthetic route to new *O*-aryl hydrogen arylphosphonodithioates containing pharmacophoric aryl fragments.

EXPERIMENTAL

The IR spectra were recorded in the range from 400 to 4000 cm^{-1} on a Bruker Vector 22 spectrometer with Fourier transform. The ^{1}H, ^{13}C, and ^{13}C–{^{1}H} NMR spectra were recorded on a Bruker Avance-600 spectrometer (600 MHz for ^{1}H and 100.6 MHz for ^{13}C) from solutions in $CDCl_3$ or acetone-d_6 using the residual proton signal of the solvent as reference. The ^{31}P NMR spectra were measured on a Bruker Avance-400 instrument (161.98 MHz) relative to 85% H_3PO_4 as external standard. The mass spectra (electron impact, 70 eV) were obtained on a Thermo Electron Corporation DFS mass spectrometer.

***O*-[4-*(*Acetylamino)phenyl] hydrogen (3,5-di-*tert*-butyl-4-hydroxyphenyl)phosphonodithioate (IIIa).** Compound **Ia**, 1.0 g (1.7 mmol), was added in portions under stirring at 20°C in a stream of dry argon to a solution of 0.5 g (3.3 mmol) of paracetamol (**II**) in a mixture of 15 mL of anhydrous chloroform and 10 mL of anhydrous benzene. The mixture was stirred for 2 h at 20°C, left to stand for 12 h, and filtered. The filtrate was evaporated at 40°C under reduced pressure (1 h at 0.5 mm and 1 h at 0.02 mm). Yield 1.3 g (87%), mp 88–90°C. IR spectrum (KBr), ν, cm^{-1}: 3616 m (O–H), 3424 m, v.br (N–H), 3257 m, br (δN–H)], 2959 s, 2927 m, 2871 m ($\nu_{as,\ s}CH_3$), 2367 w (S–H), 1629 m (C=O, amide I), 1587 m (δNH, amide II), 1609 m, 1532 m, 1505 m (C=C_{arom}), 1430 v.s ($\delta_{as}CH_3$), 1366 s (δ_sCH_3), 1016 m (PO–C), 939 m, 908 v.s, br (O–C), δOC–C_{arom}), 657 m (P=S), 534 m (P–S). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.51 s (18H, *t*-Bu), 2.21 s (3H, CH_3CO), 2.36 m (1H, HO), 7.30–7.82 m (4H, C_6H_4), 7.97 d (2H, C_6H_2, $^3J_{HH}$ = 7.8 Hz). ^{31}P–{^{1}H} NMR spectrum (C_6H_6): δ_P 89.7 ppm. Mass spectrum: *m*/*z* 451.26 (I_{rel} 1%) $[M]^{+\cdot}$. Found, %: C 58.53; H 6.97; N 2.99; P 6.67; S 14.54. $C_{22}H_{30}NO_3PS_2$. Calculated, %: C 58.51; H 6.70; N 3.10; P 6.86; S 14.20. *M* 451.58.

***O*-[4-(Acetylamino)phenyl] hydrogen 4-phenoxyphenylphosphonodithioate (IIIb)** was synthesized in a similar way. Yield 56%, mp 70–72°C. IR spectrum (mineral oil), ν, cm^{-1}: 3299 m, br (N–H), 3192 m (δN–H), 2250 w (S–H), 1661 m (C=O, amide I], 1583 s (δN–H), amide II), 1530 m (C=C_{arom}), 1468 m ($\delta_{as}CH_3$), 1017 m (PO–C), 905 m, br (O–C), (δOC–C_{arom}), 694 m (P=S), 520 m (P–S). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.65 s (3H, CH_3), 6.76–8.01 m (13H, H_{arom}). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm (the multiplicity of the corresponding signal in the proton-decoupled spectrum is given in parentheses): 34.5 q (s) (CH_3, $^1J_{HC}$ = 129.3 Hz), 114.3 d.d (d) ($C^{m'}$, $^1J_{HC}$ = 148.0, $^3J_{PC}$ = 32.6 Hz), 117.2 d.d (d) ($C^{o''}$, $^1J_{HC}$ = 148.2 Hz), 119.4 d.d (d) (C^{m}, $^1J_{HC}$ = 160.9 Hz), 121.2 d.d (d) (C^{o}, $^1J_{HC}$ = 163.5, $^3J_{PC}$ = 40.7 Hz), 121.5 d (s) ($C^{p''}$, $^1J_{HC}$ = 163.0 Hz), 124.1 d (d) ($C^{i'}$, $^1J_{PC}$ = 65.0 Hz), 127.8 d (s) (C^{p}, $^1J_{HC}$ = 158.8 Hz), 128.9 d (s) ($C^{m''}$, $^1J_{HC}$ = 160.2 Hz), 132.7 d.d (d) ($C^{o'}$, $^1J_{HC}$ = 168.6, $^2J_{PC}$ = 13.0 Hz), 136.0 d (d) (C^{i}, $^3J_{PC}$ = 49.8 Hz), 155.3 s (s) ($C^{i''}$), 160.6 s (s) ($C^{p'}$), 167.4 s (s) (C=O). ^{31}P–{^{1}H} NMR spectrum (C_6H_6): δ_P 78.9 ppm. Mass spectrum: *m*/*z* 415.91 (I_{rel} 2%) $[M]^{+\cdot}$. Found, %: C 57.87; H 4.74; N 3.57; P 7.34; S 15.57. $C_{20}H_{18}NO_3PS_2$. Calculated, %: C 57.82; H 4.37; N 3.37; P 7.46; S 15.44. *M* 415.47.

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